Nationwide analysis of treatment outcomes in children and adolescents routinely treated for tuberculosis in the Netherlands

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High success rates for TB treatment were achieved in children and adolescents in the Netherlands. To further optimise care in this population, several risk factors particularly associated with mortality and loss to follow-up have been identified. http://bit.ly/2lLJRTC

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ABSTRACT

Background: As a vulnerable population, children and adolescents with tuberculosis (TB) are faced with many challenges, even those who live in low TB incidence countries. We aimed to evaluate factors associated with TB treatment outcomes allowing more focused interventions to support this population once diagnosed.

Methods: A retrospective cohort study using a nationwide surveillance database was performed in children and adolescents (aged 0–18 years) treated for TB in the Netherlands from 1993 to 2018. Logistic regression analyses were used to estimate adjusted odds ratios (aOR) for associated factors of mortality and loss to follow-up (LTFU).

Results: Among 3253 eligible patients with known outcomes, 94.4% (95.9% children and 92.8% adolescents) were cured or completed treatment, 0.7% died during treatment and 4.9% were LTFU. There were no reported treatment failures. Risk factors of death included children aged 2–4 years (aOR 10.42), central nervous system TB (aOR 5.14), miliary TB (aOR 10.25), HIV co-infection (aOR 8.60), re-treated TB cases (aOR 10.12) and drug-induced liver injury (aOR 6.50). Active case-finding was a protective factor of death (aOR 0.13). Risk factors of LTFU were adolescents aged 15–18 years (aOR 1.91), illegal immigrants (aOR 4.28), urban domicile (aOR 1.59), unknown history of TB contact (aOR 1.99), drug-resistant TB (aOR 2.31), single adverse drug reaction (aOR 2.12), multiple adverse drug reactions (aOR 7.84) and treatment interruption >14 days (aOR 6.93). Treatment in recent years (aOR 0.94) and supervision by public health nurses (aOR 0.14) were protective factors of LTFU.

Conclusion: Highly successful treatment outcomes were demonstrated in children and adolescents routinely treated for TB. Special attention should be given to specific risk groups to improve treatment outcomes.

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Introduction

Tuberculosis (TB) is a major global health problem with an estimated 1 million children worldwide developing TB in 2017 [1]. Childhood TB has historically been given low priority in most national programmes because it contributes little to disease transmission. Similarly, adolescents are faced with many challenges as they have been neglected in TB surveillance, even when they suffer a significant burden of the disease [2, 3]. Since the World Health Organization (WHO) published 10 key actions in 2013 as the first roadmap for childhood TB [4], significant progress has been made, but gaps still remain, especially in age- and disease-related challenges such as young children (aged <5 years), adolescents (aged 10–19 years), TB/HIV co-infection and multidrug-resistant (MDR)-TB. The 2018 WHO roadmap brings new hope of accelerating efforts towards ending TB in children and adolescents by ensuring that they receive high priority in all TB prevention and control activities [5].

As one of the top 10 causes of death, childhood TB is a silent killer, with the risk of mortality being particularly high in children aged <5 years and HIV co-infected children not receiving antiretroviral therapy (ART) [6, 7]. In low-incidence countries like the Netherlands, TB elimination requires extensive yet focused screening and prevention as the patients become more concentrated in certain vulnerable and high-risk groups such as the poor, immigrants, asylum seekers, homeless, prisoners, alcohol or drug addicts and people living with HIV/AIDS [8]. Management of childhood and adolescent TB is still a pressing challenge even for low-incidence countries, particularly due to the lack of child-friendly drug formulations, difficulties in diagnosis and treatment of latent TB infection (LTBI) [9].

A few studies with large cohorts of children, mostly from high-incidence settings in Africa, have reported factors associated with TB treatment outcomes in children [10–14]. However, most of the variables analysed in these studies were relatively limited to demographic and clinical characteristics. Other potential confounders such as vaccination status, types of case-finding, drug-susceptibility of the TB strains and other clinical-, bacteriological- and treatment-related factors have not been fully evaluated. In addition, related data in both children and adolescents from low-incidence countries are lacking. In this context, our study aimed to evaluate treatment outcomes and associated factors in children and adolescents routinely treated for TB in the Netherlands. This would allow for appropriate interventions to optimise TB care in this vulnerable population.

Methods

Study design and data sources

This retrospective cohort study was performed using surveillance data obtained from the Netherlands Tuberculosis Register. The Netherlands Tuberculosis Register is a nationwide database for patients with TB and LTBI, managed by the Dutch National Institute for Public Health and the Environment (RIVM) in collaboration with 25 departments of the Municipal Public Health Services (MPHS) and the Royal Netherlands Tuberculosis Association (KNCV). Since 1993, data on disease notification, demographics, clinical, bacteriological and treatment characteristics are recorded by the MPHS in all TB patients.

Study population

All children and adolescents (aged 0–18 years) treated for TB between January 1993 and December 2018 were included in this study. Patients in ongoing treatment with incomplete data on treatment outcomes were excluded.

Data collection

The following individual data with anonymous identifiers were obtained from the Netherlands Tuberculosis Register on May 22 2019: 1) demographics (year of diagnosis, age, sex, native/foreign-born,

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WHO region of birth, immigrant status and living area); 2) TB notification and clinical characteristics (types of case-finding, history of TB contact, travel history in TB-endemic area, site and localisation of TB, cavitary TB, bacille Calmette–Guérin (BCG) vaccination, TB symptoms, patient's and doctor's delay in diagnosis and treatment, and comorbidity); 3) bacteriological characteristics (acid-fast bacilli smear microscopy, mycobacterial culture and drug susceptibility testing (DST)); and 4) treatment characteristics (previous history of TB/LTBI treatment, daily/intermittent dosing, presence of adverse drug reactions (ADRs), drug-induced liver injury (DILI), treatment interruption >14 days, hospitalisation, treatment supervision by public health nurses (PHNs) and implementation of directly observed therapy).

Definitions

Age was generally divided into two groups: children aged <15 years and adolescents aged 15–18 years. The cut-off of <15 years for children was used to be consistent with the age category used for reporting TB surveillance data nationally and by the WHO [1]. The upper age limit of 18 years for adolescent TB was based on the definition used by the WHO European region [15]. Active case-finding was defined as the systematic screening for active TB cases in a predetermined high-risk group for TB, rather than waiting for patients who came on their own to the healthcare system because of TB symptoms (passive case-finding). Pulmonary TB included all forms of TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB and other specified respiratory TB. TB within other locations in the body than the lungs, including mediastinal lymphadenopathy, were classified as extrapulmonary TB (EPTB), which may have involved isolated EPTB or a combination of pulmonary TB and EPTB. Confirmed drug-susceptible TB was defined as a susceptible result of DST for all first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), while presumed drug-susceptible TB was defined as patients treated with first-line anti-TB drugs without sufficient information on DST. Patients with DST results of monoresistant, polyresistant, MDR- or extensively drug-resistant (XDR)-TB were classified as confirmed drug-resistant TB. DILI due to anti-TB drugs was defined as an increased level of alanine aminotransferase more than three times the upper limit of normal in the presence of symptoms of hepatotoxicity or more than five times the upper limit of normal in the absence of symptoms. Treatment supervision by PHNs was defined as supportive discussions with patients and their family to provide TB education and identification of obstacles that influence treatment adherence. Directly observed therapy was defined as every dose of anti-TB drugs taken under direct observation for a period of time, provided by either PHNs or other selected third parties such as family members or home nursing services. Operational definitions for all variables are shown in supplementary table S1 [16, 17].

Outcomes

Treatment outcomes (cured, treatment completed, died, treatment failed, lost to follow-up (LTFU), and not evaluated (unknown outcomes)) were defined based on the Dutch national guidelines for TB programmes and generally in accordance with the current WHO guidelines (table 1) [16, 18].

Data analysis

Associations of patient characteristics with mortality and LTFU were evaluated. First, patients who died during treatment were compared to those who were alive at the end of treatment regardless of whether they were cured, completed or failed treatment; this definition excluded LTFU and unknown outcomes. Second, LTFU patients were compared to those who achieved cure or completed treatment with or without evidence of treatment failure; this definition excluded death and unknown outcomes. Given the possibility of selection bias from the exclusion of particular patients in the first and second analyses, additional outcome classification was created assessing patients who achieved cure or completed treatment (favourable) compared to all other outcomes (unfavourable).

Univariate and multivariate logistic regression analyses were used to evaluate the association between candidate variables and treatment outcomes. All variables in the univariate analysis showing a trend towards association with each of the evaluated outcomes, and with a minimum number of 20 patients in any particular group of predictors, were eligible for inclusion in multivariate analysis and were selected using backward elimination. The final multivariate models retained all explanatory variables with a p-value <0.1. The Hosmer–Lemeshow test was used to evaluate the goodness of fit of the final models. The performance of the final models was measured by the area under the receiver operating characteristic curve. Crude and adjusted odds ratios (aORs) with 95% confidence intervals were used to estimate the association between explanatory variables and treatment outcomes. Statistical significance was accepted at $p<0.05$, whereas p-values of 0.05–0.10 were considered trends. All data were analysed using SPSS Statistics (version 25.0; IBM, Armonk, NY, USA).

TABLE 1 Treatment outcome definitions used in this study

	Definition for drug-susceptible TB	Definition for drug-resistant TB
Cured	A patient who had completed a full course of therapy or ⩾80% of the prescribed doses with a confirmed culture-negative result at the end of treatment	A patient who had treatment completed without evidence of failure with three or more consecutive negative cultures taken ⩾30 days apart after the intensive phase
Treatment completed	A patient who had taken all of the prescribed doses or ⩾80% of them without any information on sputum culture at the end of treatment	A patient who had treatment completed without evidence of failure, but no record that three or more consecutive cultures taken ⩾30 days apart were negative after the intensive phase
Died	A patient who died for any reason before starting or during the course of treatment	A patient who died for any reason during the course of treatment
Treatment failed	A patient whose sputum culture was positive after 5 months or later during treatment	A patient who met one of the following criteria: lack of conversion by the end of the intensive phase; bacteriological reversion in the continuation phase after conversion to negative; evidence of additional acquired resistance to fluoroquinolone or second-line injectable drugs; or evidence of adverse drug reactions requiring discontinuation of treatment
Lost to follow-up	A patient who met one of the following criteria: treatment interruption for two consecutive months or more; treatment completion of <80% of the prescribed doses; treatment incompletion of 6 months within the 9-month treatment period; or treatment incompletion of 9 months within the 12-month treatment period	A patient whose treatment was interrupted for two consecutive months or more
Not evaluated (unknown)	A patient for whom no treatment outcome (cured, treatment completed, died, treatment failed and LTFU) was assigned in the database; this included cases "transferred out" to another unit (country) with unknown treatment results	A patient for whom no treatment outcome was assigned in the database; this included cases "transferred out" to another unit (country) with unknown treatment results
Treatment success	The sum of "cured" and "treatment completed"	The sum of "cured" and "treatment completed"

TB: tuberculosis; LTFU: lost to follow-up. Drug-resistant TB comprised monoresistant TB (resistance to one first-line anti-TB drug only), polyresistant TB (resistance to more than one first-line anti-TB drug other than isoniazid and/or rifampicin), multidrug-resistant (MDR)-TB (resistance to at least both isoniazid and rifampicin), extensively drug-resistant TB (resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition to MDR-TB), and rifampicin-resistant TB (resistance to rifampicin with or without resistance to other anti-TB drugs) [16, 18].

Ethics

Research approval was granted by the research committee of the Netherlands Tuberculosis Register. As this was a retrospective study using routine data collected anonymously, ethics clearance and individual patient written informed consent were not required under Dutch law.

Results

During a 26-year period from January 1993 to December 2018, 3442 TB cases in children and adolescents were notified: 46 patients in ongoing treatment were excluded. Of 3396 eligible patients (1764 (51.9%) children and 1632 (48.1%) adolescents), 1893 (55.7%) were male, 2017 (59.4%) were foreign-born and 1454 (42.8%) had pulmonary TB. Mycobacterial culture was performed in 2261 (66.6%) of the eligible patients with 1921 (56.6%) being culture-positive and 340 (10%) culture-negative. Out of 1921 patients with culture-confirmed disease, 1610 (83.8%) had information on species. Of these, 1523 (94.6%) had *Mycobacterium tuberculosis* and 87 (5.4%) had other *M. tuberculosis* complex. None of the patients were identified as nontuberculous mycobacterial infections. Most of the patients (n=2625, 77.3%) were treated as presumed drug-susceptible TB, 591 (17.4%) as confirmed drug-susceptible TB and 180 (5.3%) as confirmed drug-resistant TB (table 2). Severe forms of TB (central nervous system (CNS) or miliary TB) were notified in 100 (2.9%) out of 3396 eligible patients: 33 (33%) had received BCG vaccination and 44 (44%) were not BCG-vaccinated. Out of 44 severe cases who were not BCG-vaccinated, 23 (52.3%) were children aged <5 years, 15 (34.1%) were children aged 5–14 years and the remaining six (13.6%) were adolescents.

By including patients with both known and unknown outcomes, overall success rates of 92.0% and 88.7% were shown in children and adolescents, respectively. Known outcomes were recorded in 3253 (95.8%) out of 3396 eligible patients. Of these, success rates were 95.9% in children and 92.8% in adolescents (table 2).

TABLE 2 Characteristics of children and adolescents treated for tuberculosis (TB) in the Netherlands

	Total cases	<5 years	5–14 years	15–18 years
Cases n	3396	638	1126	1632
Year of diagnosis				
1993–1998	1092 (32.2)	218 (34.2)	400 (35.5)	474 (29.0)
1999–2003	1005 (29.6)	173 (27.1)	270 (24.0)	562 (34.4)
2004–2008	485 (14.3)	110 (17.2)	177 (15.7)	198 (12.1)
2009–2013	398 (11.7)	79 (12.4)	151 (13.4)	168 (10.3)
2014–2018	416 (12.2)	58 (9.1)	128 (11.4)	230 (14.1)
Sex				
Male	1893 (55.7)	337 (52.8)	525 (46.6)	1031 (63.2)
Female	1503 (44.3)	301 (47.2)	601 (53.4)	601 (36.8)
Born in the Netherlands				
Yes	1350 (39.8)	502 (78.7)	522 (46.4)	326 (20.0)
No	2017 (59.4)	130 (20.4)	594 (52.8)	1293 (79.2)
Unknown	29 (0.9)	6 (0.9)	10 (0.9)	13 (0.8)
Site of TB				
Pulmonary TB	1454 (42.8)	229 (35.9)	401 (35.6)	824 (50.5)
EPTB	1570 (46.2)	352 (55.2)	600 (53.3)	618 (37.9)
Pulmonary TB + EPTB	372 (11.0)	57 (8.9)	125 (11.1)	190 (11.6)
Reason for TB investigation				
Presentation of TB symptoms	1582 (46.6)	178 (27.9)	478 (42.5)	926 (56.7)
Contact investigation	944 (27.8)	343 (53.8)	429 (38.1)	172 (10.5)
Screening high-risk groups	620 (18.3)	61 (9.6)	162 (14.4)	397 (24.3)
Others	35 (1.0)	12 (1.9)	11 (1.0)	12 (0.7)
Unknown	215 (6.3)	44 (6.9)	46 (4.1)	125 (7.7)
AFB smear microscopy (sputum or BAL)				
Negative	570 (16.8)	51 (8.0)	158 (14.0)	361 (22.1)
Noncavitary TB	515 (15.2)	48 (7.5)	147 (13.0)	320 (19.6)
Cavitary TB	25 (0.7)	1 (0.1)	4 (0.3)	20 (1.2)
Positive	534 (15.7)	26 (4.1)	121 (10.7)	387 (23.7)
Noncavitary TB	324 (9.5)	23 (3.6)	73 (6.5)	228 (14.0)
Cavitary TB	187 (5.5)	2 (0.3)	43 (3.8)	142 (8.7)
Unknown/not done	2292 (67.5)	561 (87.9)	847 (75.2)	884 (54.2)
Mycobacterial culture				
Negative	340 (10.0)	60 (9.4)	130 (11.5)	150 (9.2)
Positive	1921 (56.6)	195 (30.6)	506 (44.9)	1220 (74.8)
Unknown/not done	1135 (33.4)	383 (60.0)	490 (43.5)	262 (16.1)
Drug susceptibility testing				
Confirmed drug-susceptible TB	591 (17.4)	46 (7.2)	144 (12.8)	401 (24.6)
Presumed drug-susceptible TB	2625 (77.3)	568 (89.0)	936 (83.1)	1121 (68.7)
Culture positive, DST unknown	1150 (33.9)	125 (19.6)	316 (28.1)	709 (43.4)
Culture negative or unknown	1475 (43.4)	443 (69.4)	620 (55.1)	412 (25.2)
Confirmed drug-resistant TB	180 (5.3)	24 (3.8)	46 (4.1)	110 (6.7)
Mono/poly H	131 (3.9)	20 (3.1)	33 (2.9)	78 (4.8)
Mono/poly R	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Mono Z	14 (0.4)	3 (0.5)	4 (0.4)	7 (0.4)
MDR-TB	32 (0.9)	1 (0.2)	9 (0.8)	22 (1.3)
XDR-TB	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Treatment outcomes (uncorrected)				
Cured/completed	3071 (90.4)	577 (90.4)	1046 (92.9)	1448 (88.7)
LTFU	160 (4.7)	24 (3.8)	34 (3.0)	102 (6.3)
Failed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Died	22 (0.6)	9 (1.4)	3 (0.3)	10 (0.6)
Not evaluated (unknown)	143 (4.2)	28 (4.4)	43 (3.9)	72 (4.4)
Treatment outcomes (corrected)[#]				
Total n	3253	610	1083	1560
Cured/completed	3071 (94.4)	577 (94.6)	1046 (96.6)	1448 (92.8)
LTFU	160 (4.9)	24 (3.9)	34 (3.1)	102 (6.5)
Failed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Died	22 (0.7)	9 (1.5)	3 (0.3)	10 (0.6)

Data are presented as n (%), unless otherwise stated. EPTB: extrapulmonary tuberculosis; AFB: acid-fast bacilli; BAL: bronchoalveolar lavage; DST: drug susceptibility testing; H: isoniazid; R: rifampicin; Z: pyrazinamide; MDR: multidrug-resistant; XDR: extensively drug-resistant; LTFU: lost to follow-up. [#]: excluded patients with unknown outcomes.

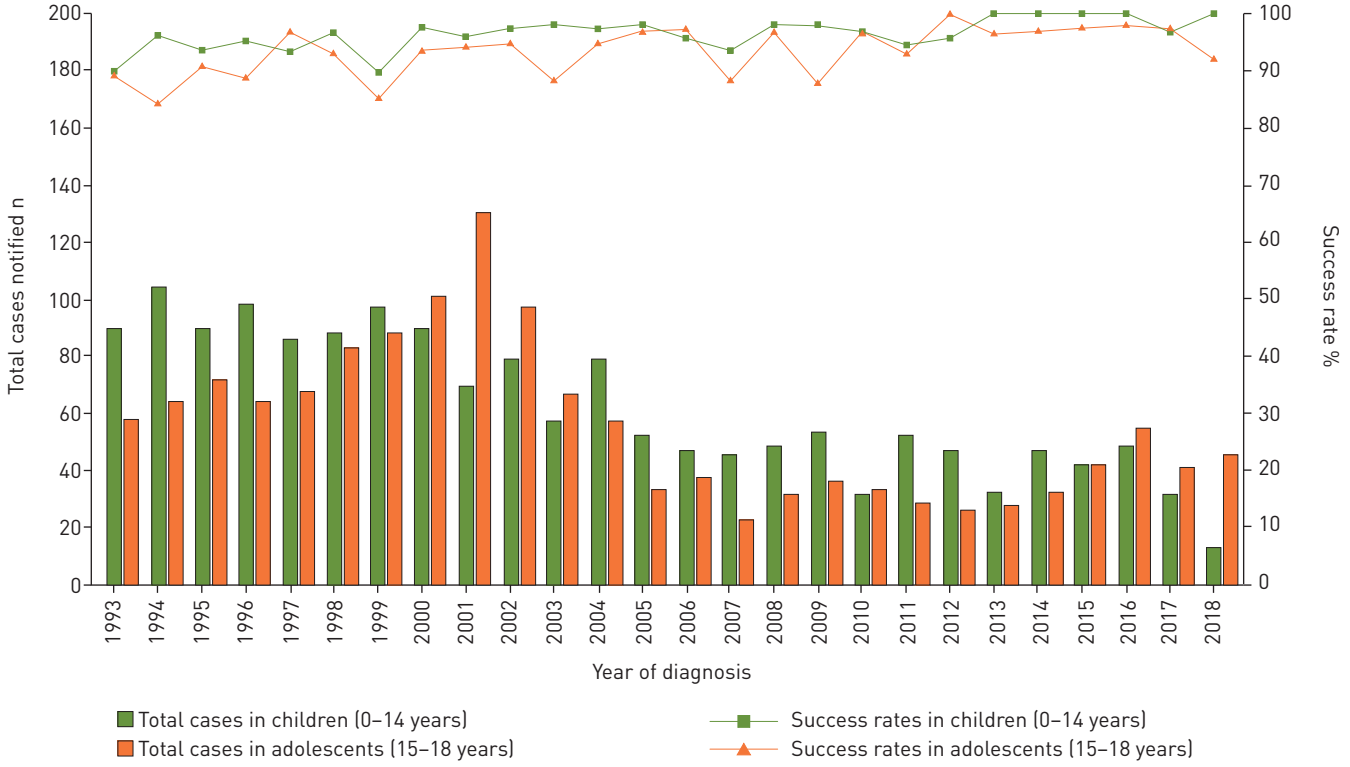

FIGURE 1 Notified tuberculosis cases and trend of success rates among children and adolescents treated for tuberculosis in the Netherlands, 1993–2018.

Annual success rates in children were constantly >90% over the years from 1993 to 2018, and relatively higher compared to adolescents (figure 1). LTFU was higher in adolescents (n=102, 6.5%) than children (n=58, 3.4%). No treatment failure was reported and 22 (0.7%) out of all patients died during treatment (table 2). Case fatality rates for other subpopulations are presented in supplementary table S2.

Our multivariate model showed that children aged 2–4 years had an increased odds of death compared to children aged 5–14 years (aOR 10.42, 95% CI 2.25–48.36). In addition, positive associations with mortality were shown in patients with CNS TB (aOR 5.14, 95% CI 1.17–22.62), miliary TB (aOR 10.25, 95% CI 2.30–45.67), HIV co-infection (aOR 8.60, 95% CI 1.57–47.24), re-treated TB cases (aOR 10.12, 95% CI 1.54–66.47) and those who developed DILI during therapy (aOR 6.50, 95% CI 1.09–38.71). Active case-finding was associated with lower odds of death compared to passive case-finding (aOR 0.13, 95% CI 0.03–0.66) (table 3). Patients with unknown history of TB contact, unknown BCG status, who experienced TB symptoms or were hospitalised for ⩾1 week during treatment had a significantly increased odds of death in univariate analysis, but did not remain significant in multivariate analysis (supplementary table S3). Although unknown history of TB contact was not sustained in multivariate analysis as a predictor of mortality, it was significantly associated with higher odds of either patient's delay (aOR 2.36, 95% CI 1.46–3.80) or doctor's delay (aOR 4.29, 95% CI 2.48–7.42) compared to known TB contact history, adjusted for age, sex, smear microscopy and sites of TB.

Several factors were associated with higher odds of LTFU, including adolescence (aOR 1.91, 95% CI 1.25–2.93), illegal immigrants (aOR 4.28, 95% CI 1.60–11.42), urban domicile (aOR 1.59, 95% CI 1.10–2.29), unknown history of TB contact (aOR 1.99, 95% CI 1.19–3.34), confirmed drug-resistant TB (aOR 2.31, 95% CI 1.05–5.10), single ADR (aOR 2.12, 95% CI 1.18–3.83), multiple ADRs (aOR 7.84, 95% CI 3.55–17.33) and treatment interruption lasting >14 days (aOR 6.93, 95% CI 2.72–17.63). Treatment in recent years (aOR 0.94, 95% CI 0.89–0.98) and treatment supervision by PHNs (aOR 0.14, 95% CI 0.07–0.29) were associated with lower odds of LTFU (table 4). Being male and foreign-born were significantly associated with higher odds of LTFU in univariate analysis, but not found to be statistically significant in multivariate analysis (supplementary table S4). However, our subgroup analysis identified that male foreign-born adolescents had a significantly increased odds of LTFU compared to female foreign-born adolescents (aOR 2.31, 95% CI 1.30–4.10), adjusted for year of diagnosis, area of living, DST results, presence of ADRs, treatment interruption lasting >14 days and treatment supervision by PHNs.

TABLE 3 Final model for factors associated with mortality in children and adolescents treated for tuberculosis (TB) in the Netherlands

	Dead	Alive[#]	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Cases n	22	3071				
Age						
<2 years	2 (9.1)	220 (7.2)	3.17 (0.53–19.08)	0.208	1.22 (0.16–9.56)	0.846
2–4 years	7 (31.8)	357 (11.6)	6.84 (1.76–26.58)	0.006	10.42 (2.25–48.36)	0.003
5–14 years	3 (13.6)	1046 (34.1)	1.00		1.00	
15–18 years	10 (45.5)	1448 (47.2)	2.41 (0.66–8.77)	0.183	1.13 (0.27–4.77)	0.863
Type of case-finding						
Passive	15 (68.2)	1478 (48.1)	1.00		1.00	
Active	2 (9.1)	1511 (49.2)	0.13 (0.03–0.57)	0.007	0.13 (0.03–0.66)	0.014
Unknown	5 (22.7)	82 (2.7)	6.01 (2.13–16.93)	0.001	5.41 (1.36–21.44)	0.016
Main localisation of TB						
Lungs	8 (36.4)	1302 (42.4)	1.00		1.00	
CNS	4 (18.2)	49 (1.6)	13.29 (3.87–45.62)	<0.001	5.14 (1.17–22.62)	0.030
Miliary	6 (27.3)	35 (1.1)	27.90 (9.19–84.70)	<0.001	10.25 (2.30–45.67)	0.002
Others	0 (0.0)	1556 (50.7)	n/a	0.987	n/a	0.986
Unknown	4 (18.2)	129 (4.2)	5.05 (1.50–16.99)	0.009	3.51 (0.89–3.89)	0.074
HIV status						
No/unknown	18 (81.8)	3039 (99.0)	1.00		1.00	
HIV positive	4 (18.2)	32 (1.0)	21.10 (6.76–65.86)	<0.001	8.60 (1.57–47.24)	0.013
Previously treated for TB						
No	13 (59.1)	2796 (91.0)	1.00		1.00	
Yes	2 (9.1)	60 (2.0)	7.17 (1.58–32.47)	0.011	10.12 (1.54–66.47)	0.016
Unknown	7 (31.8)	215 (7.0)	7.00 (2.76–17.73)	<0.001	7.89 (2.31–26.92)	0.001
Type of ADR						
No/unknown	19 (86.4)	2900 (94.4)	1.00		1.00	
DILI	2 (9.1)	54 (1.8)	5.65 (1.28–24.87)	0.022	6.50 (1.09–38.71)	0.040
Others	1 (4.5)	117 (3.8)	1.30 (0.17–9.83)	0.796	0.99 (0.11–8.81)	0.992

Data are presented as n (%), unless otherwise stated. cOR: crude odds ratio; aOR: adjusted odds ratio; CNS: central nervous system; ADR: adverse drug reaction; DILI: drug-induced liver injury; n/a: not applicable. Hosmer–Lemeshow test p=0.976; area under the receiver operating characteristic curve 0.96 (95% CI 0.94–0.99). [#]: included patients who achieved cure or completed treatment and excluded those who were lost to follow-up or with unknown outcomes.

The following factors were associated with higher odds of unfavourable outcome: children aged <5 years (aOR 1.58, 95% CI 1.02–2.46), adolescence (aOR 1.56, 95% CI 1.11–2.19), illegal immigrants (aOR 5.10, 95% CI 2.15–12.10), unknown history of TB contact (aOR 2.00, 95% CI 1.30–3.07), miliary TB (aOR 3.37, 95% CI 1.42–8.03), multiple ADRs (aOR 7.54, 95% CI 3.56–15.99) and treatment interruption lasting >14 days (aOR 4.90, 95% CI 2.10–11.42). Treatment supervision by PHNs was associated with lower odds of unfavourable outcome (aOR 0.08, 95% CI 0.05–0.15) (table 5). Results of the univariate analysis for unfavourable outcome are presented in supplementary table S5.

Discussion

An overall high success rate of 92.0% in children was recorded in our study, although this included children with unknown outcomes. This is relatively comparable with studies of children from other low-incidence countries such as Australia (89.4%) and the UK (88.0%) [19, 20]. A high success rate was also recorded in adolescents: comparable data from other low-incidence countries are lacking. This underlines that adolescents are often neglected in TB surveillance reports [3, 5]. The low mortality rate of <1% in our study is similar to those reported in the UK and Australia [19, 20], but is lower compared to various reports from high-incidence countries in Asia and Africa (3–17%) [11–14]. Interestingly, a recent study from South Africa also reported <1% mortality rate in children; however, this number was probably higher, as children with severe forms of TB admitted to hospital may have died before diagnosis or after diagnosis but prior to recording in the database [10].

Several risk factors of mortality are shown in our study including children aged 2–4 years, CNS TB, miliary TB, HIV co-infection, re-treated TB cases and cases with DILI. Overall, the increased risk of death in children aged <5 years is consistent with those reported in a meta-analysis and a modelling study [6, 7]. However, in contrast to earlier findings from South Africa [10], our results did not confirm the risk of death in a subgroup of children aged <2 years. In children aged <2–3 years, the progression of primary

TABLE 4 Final model for factors associated with loss to follow-up (LTFU) in children and adolescents treated for tuberculosis (TB) in the Netherlands

	LTFU	Non-LTFU[#]	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Cases n	160	3071				
Year of diagnosis median (IQR)	1999 (1995–2003)	2001 (1997–2009)	0.94 (0.92–0.97)	<0.001	0.94 (0.89–0.98)	0.011
Age						
<5 years	24 (15.0)	577 (18.8)	1.28 (0.75–2.18)	0.364	1.47 (0.84–2.59)	0.178
5–14 years	34 (21.3)	1046 (34.1)	1.00		1.00	
15–18 years	102 (63.7)	1448 (47.2)	2.17 (1.46–3.22)	<0.001	1.91 (1.25–2.93)	0.003
Immigrants or asylum seekers						
No	51 (31.9)	1261 (41.1)	1.00		1.00	
Yes, duration <2.5 years	71 (44.4)	1139 (37.1)	1.54 (1.07–2.23)	0.021	1.15 (0.73–1.81)	0.549
Yes, illegal immigrants	8 (5.0)	22 (0.7)	8.99 (3.82–21.17)	<0.001	4.28 (1.60–11.42)	0.004
Yes, duration ⩾2.5 years	17 (10.6)	502 (16.3)	0.84 (0.48–1.46)	0.533	0.59 (0.32–1.10)	0.099
Yes, duration unknown	13 (8.1)	147 (4.8)	2.19 (1.16–4.12)	0.015	1.32 (0.65–2.66)	0.443
Area of living						
Urban[¶]	59 (36.9)	854 (27.8)	1.52 (1.09–2.11)	0.014	1.59 (1.10–2.29)	0.014
Suburban[+]	101 (63.1)	2217 (72.2)	1.00		1.00	
Known history of TB contact						
No	135 (84.4)	2090 (68.1)	2.53 (1.64–3.91)	<0.001	1.99 (1.19–3.34)	0.009
Yes	25 (15.6)	981 (31.9)	1.00		1.00	
Drug susceptibility						
Confirmed drug-susceptible TB	16 (10.0)	552 (18.0)	1.00		1.00	
Presumed drug-susceptible TB	127 (79.4)	2365 (77.0)	1.85 (1.09–3.14)	0.022	1.38 (0.72–2.64)	0.332
Confirmed drug-resistant TB	17 (10.6)	154 (5.0)	3.81 (1.88–7.71)	<0.001	2.31 (1.05–5.10)	0.038
Presence of ADR						
No/unknown	130 (81.3)	2900 (94.4)	1.00		1.00	
Yes, single ADR	19 (11.9)	147 (4.8)	2.88 (1.73–4.80)	<0.001	2.12 (1.18–3.83)	0.012
Yes, multiple ADRs	11 (6.9)	24 (0.8)	10.22 (4.90–21.32)	<0.001	7.84 (3.55–17.33)	<0.001
Treatment interruption >14 days						
No	20 (12.5)	1045 (34.0)	1.00		1.00	
Yes	10 (6.3)	42 (1.4)	12.44 (5.48–28.23)	<0.001	6.93 (2.72–17.63)	<0.001
Unknown	130 (81.3)	1984 (64.6)	3.42 (2.13–5.51)	<0.001	1.03 (0.45–2.35)	0.938
Supervision by PHNs						
No	12 (7.5)	34 (1.1)	1.00		1.00	
Yes	141 (88.1)	2976 (96.9)	0.13 (0.07–0.26)	<0.001	0.14 (0.07–0.29)	<0.001
Unknown	7 (4.4)	61 (2.0)	0.32 (0.12–0.90)	0.031	0.21 (0.07–0.64)	0.006

Data are presented as n (%), unless otherwise stated. cOR: crude odds ratio; aOR: adjusted odds ratio; IQR: interquartile range; ADR: adverse drug reaction; PHNs: public health nurses. Hosmer–Lemeshow test p=0.745; area under the receiver operating characteristic curve 0.75 (95% CI 0.72–0.79). [#]: included patients who achieved cure or completed treatment and excluded those who died or with unknown outcomes; [¶]: the Hague, Utrecht (city), Amsterdam and Rotterdam; [+]: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas.

infection into severe disease (CNS or miliary TB) is more frequent [21]. These severe forms of disease were associated with mortality in our study, independent to the age of the patients. In high-incidence countries, BCG vaccination has been reported as a highly cost-effective intervention to prevent CNS TB and miliary TB [22]. In the Netherlands, BCG vaccination is only targeted to newborns with a parent coming from a country with estimated TB incidence >50 per 100 000 population, and offered to immigrants aged <12 years with no evidence of BCG vaccination at pre-entry TB screening [23]. Notably, more patients with severe disease in our study were not BCG-vaccinated: half of them were aged <5 years. These results support the previous recommendation by Erkens *et al.* [24] to improve the coverage of BCG vaccination among eligible risk groups in the Netherlands.

The role of TB/HIV co-infection as a predictor of mortality in children is supported by various studies, mostly from HIV-endemic settings [10–13]. For TB/HIV co-infected children taking ART, the risk of death is lower than children without ART [6]. In our cohorts, ART status was not completely clear, because the Netherlands Tuberculosis Register has only recorded it since 2016. Next, a recurrent episode of TB can be due to endogenous reactivation of indolent mycobacteria (relapse) or exogenous re-infection, and the latter can be caused by MDR *M. tuberculosis* strains [25]. Two patients with recurrent TB who died in our study were classified as non-relapse patients, one of which was treated for MDR-TB. It is possible that MDR-TB plays a role in increasing the risk of mortality in recurrent cases.

TABLE 5 Final model for factors associated with unfavourable outcome in children and adolescents treated for tuberculosis (TB) in the Netherlands

	Unfavourable[#]	Favourable[¶]	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Cases n	325	3071				
Age						
<5 years	61 (16.8)	577 (18.8)	1.38 (0.98–1.96)	0.069	1.58 (1.02–2.46)	0.040
5–14 years	80 (24.6)	1046 (34.1)	1.00		1.00	
15–18 years	184 (56.6)	1448 (47.2)	1.66 (1.26–2.19)	<0.001	1.56 (1.11–2.19)	0.010
Immigrants or asylum seekers						
No	98 (30.2)	1261 (41.1)	1.00		1.00	
Yes, duration <2.5 years	134 (41.2)	1139 (37.1)	1.51 (1.15–1.99)	0.003	1.09 (0.74–1.59)	0.663
Yes, illegal immigrants	17 (5.2)	22 (0.7)	9.94 (5.11–19.34)	<0.001	5.10 (2.15–12.10)	<0.001
Yes, duration ⩾2.5 years	37 (11.4)	502 (16.3)	0.95 (0.64–1.40)	0.791	0.74 (0.45–1.20)	0.222
Yes, duration unknown	39 (12.0)	147 (4.8)	3.41 (2.27–5.14)	<0.001	1.71 (0.99–2.96)	0.054
Known TB contact history						
No	274 (84.3)	2090 (68.1)	2.52 (1.85–3.43)	<0.001	2.00 (1.30–3.07)	0.002
Yes	51 (15.7)	981 (31.9)	1.00		1.00	
Main localisation of TB						
Primary TB infection	30 (9.2)	673 (21.9)	0.54 (0.36–0.82)	0.004	0.85 (0.52–1.41)	0.534
Lungs	107 (32.9)	1302 (42.4)	1.00		1.00	
Respiratory tract	18 (5.5)	388 (12.6)	0.56 (0.34–0.94)	0.029	0.67 (0.39–1.15)	0.146
CNS	7 (2.2)	49 (1.6)	1.74 (0.77–3.93)	0.184	1.52 (0.60–3.87)	0.382
Abdominal	6 (1.8)	51 (1.7)	1.43 (0.60–3.41)	0.418	1.81 (0.72–4.53)	0.207
Osteoarticular	6 (1.8)	67 (2.2)	1.09 (0.46–2.57)	0.844	1.25 (0.51–3.05)	0.629
Other organs	33 (10.2)	377 (12.3)	1.06 (0.71–1.60)	0.761	0.83 (0.53–1.31)	0.427
Miliary	9 (2.8)	35 (1.1)	3.13 (1.46–6.68)	0.003	3.37 (1.42–8.03)	0.006
Unknown	109 (33.5)	129 (4.2)	10.28 (7.45–14.19)	<0.001	3.99 (2.56–6.20)	<0.001
Previously treated for TB						
No	273 (84.0)	2796 (91.0)	1.00		1.00	
Yes	13 (4.0)	60 (2.0)	2.22 (1.20–4.09)	0.011	2.04 (0.98–4.24)	0.057
Unknown	39 (12.0)	215 (7.0)	1.86 (1.29–2.67)	0.001	1.07 (0.67–1.71)	0.765
Presence of ADR						
No/unknown	291 (89.5)	2900 (94.4)	1.00		1.00	
Yes, single ADR	20 (6.2)	147 (4.8)	1.36 (0.84–2.20)	0.216	1.57 (0.89–2.77)	0.120
Yes, multiple ADRs	14 (4.3)	24 (0.8)	5.81 (2.97–11.36)	<0.001	7.54 (3.56–15.99)	<0.001
Treatment interruption >14 days						
No	42 (12.9)	1045 (34.0)	1.00		1.00	
Yes	11 (3.4)	42 (1.4)	6.52 (3.13–13.55)	<0.001	4.90 (2.10–11.42)	<0.001
Unknown	272 (83.7)	1984 (64.6)	3.41 (2.44–4.76)	<0.001	1.58 (1.09–2.92)	0.016
Hospitalised ⩾1 week						
No/<1 week	238 (73.2)	2153 (70.1)	1.00		1.00	
Yes	68 (20.9)	815 (26.5)	0.75 (0.57–1.00)	0.050	0.71 (0.51–1.01)	0.055
Unknown	19 (5.8)	103 (3.4)	1.67 (1.01–2.77)	0.048	0.86 (0.46–1.60)	0.633
Supervised by PHNs						
No	32 (9.8)	34 (1.1)	1.00		1.00	
Yes	192 (59.1)	2976 (96.9)	0.07 (0.04–0.11)	<0.001	0.08 (0.05–0.15)	<0.001
Unknown	101 (31.1)	61 (2.0)	1.76 (0.99–3.14)	0.055	1.01 (0.51–2.00)	0.997

Data are presented as n (%), unless otherwise stated. cOR: crude odds ratio; aOR: adjusted odds ratio; CNS: central nervous system; ADR: adverse drug reaction; PHNs: public health nurses. Hosmer–Lemeshow test p=0.506; area under the receiver operating characteristic curve 0.81 (95% CI 0.78–0.84). [#]: the sum of patients who died, were lost to follow-up, or with unknown outcomes; [¶]: the sum of patients who achieved cure or completed treatment.

DILI is one of the most frequent and serious ADRs during TB therapy [26], and has been reported as a predictor of prolonged TB treatment in a Dutch setting [27]. Although a relatively lower rate of DILI was found in our study (1.8%) compared to other studies of children in Japan (8.1%) and Indonesia (15%) [28, 29], its clinical implication in increasing the risk of mortality should be taken seriously. Two studies from India and the UK reported DILI as a contributing cause of death in adult TB patients [30, 31], with the risk of mortality being even higher if accompanied by jaundice, ascites or encephalopathy [31]. Based on the current WHO guidelines for children, regular monitoring of liver function tests during TB therapy is not mandatory and only recommended if liver tenderness, hepatomegaly, jaundice or early onset of vomiting occur during treatment [32]. Given that severe hepatotoxicity can develop in patients with

asymptomatic DILI [33], regular monitoring of liver function tests as suggested for adults undergoing TB therapy might also benefit children, to improve treatment outcomes and to prevent mortality.

In the Netherlands, pre-entry LTBI screening is carried out for every immigrant and asylum seeker aged <18 years, and radiographic screening only in children aged 12–17 years from a country with TB incidence ⩾100 per 100 000 population was recently suggested [34]. The active case-finding interventions, such as screening for immigrants and asylum seekers as well as source and contact investigations have proven useful in our study to prevent mortality compared to passive case-finding. Given that unknown history of TB contact was found as a risk factor of either patient's or doctor's delay, this highlights the benefits of advocating active case-finding for early diagnosis and early treatment (including preventive therapy), in order to prevent deterioration of the disease. A large randomised controlled trial from Vietnam supports that active case-finding is a cost-effective intervention to increase TB case detection and to reduce all-cause mortality [35, 36]. In addition, a modelling study reported that household contact investigations could substantially prevent both TB cases and mortality in children [37].

For LTFU, our study identifies the following risk factors: adolescent age, illegal immigrants, unknown history of TB contact, urban domicile, confirmed drug-resistant TB, presence of ADRs and treatment interruption lasting >14 days. The increased risk of LTFU in adolescents particularly in male foreign-born adolescents might be due to the lack of awareness of the special needs of this population [15]. To improve adherence in adolescents, appropriate interventions should be understood by considering their developmental and psychosocial issues, tailoring the treatment regimen and ensuring peer and family supports [38]. Implementation of directly observed therapy in our study was not statistically significant to prevent LTFU, even in a particular subgroup of adolescents. This is supported by a meta-analysis that poor adherence in TB treatment cannot be resolved by the directly observed therapy intervention [39]. A recently published randomised controlled trial from the UK reported that smartphone-enabled video-observed therapy is more effective, preferable and cheaper than directly observed therapy for TB treatment observation [40]. In the Netherlands where internet connectivity is not an issue, video-observed therapy might also be relevant as an alternative to directly observed therapy, particularly for adolescents who have a high mobile/internet engagement. A new framework of digital health (e-health), as currently recommended by the WHO [41], might also benefit to ensure treatment adherence. Even though this e-health system has not been widely used in the Netherlands [23], it has great potential as a more patient-friendly intervention for therapy monitoring, particularly for high-risk groups and other individuals with complex confounders (*e.g.* patients living in urban areas or treated for drug-resistant TB).

Since 2005, a central web-based TB surveillance system was introduced and laboratory data were matched with the Netherlands Tuberculosis Register in real-time. These improvements might have contributed to the reduced number of LTFU cases in recent years. This is supported by our results that most of the LTFU cases (79%) were notified before 2005. The improved TB outcomes might also be related to the large number of stakeholders involved in TB control activities; from the MPHS, KNCV, RIVM and other health professionals such as pulmonary physicians, paediatricians, TB control physicians, medical microbiologists, medical technicians and PHNs [23]. Our study confirms that treatment supervision by PHNs is a protective factor of LTFU as well as an unfavourable outcome.

A particular strength of this study is a relatively wide range of variables included in the analysis from demographics to disease notification-, clinical-, bacteriological- and treatment-related factors. However, our study has several limitations that should be acknowledged. Due to the retrospective nature of the study using routine data, patient records were partly incomplete for some of the variables. Even though notification of TB is mandatory, the possibility of under-notification cases cannot be ruled out. Through a capture–recapture analysis, the adjusted under-notification of TB in 1998 was estimated to be 7.3% [42]. However, the completeness of notification is expected to have increased since 2005, when improvements were made to the Netherlands Tuberculosis Register. The high proportion of patients with presumed drug-susceptible TB in our cohorts can be explained by these changes, given that 1139 (99%) of 1150 patients with culture-confirmed disease but without information on DST results were registered before 2005. Next, our database cannot distinguish between TB contact history with an infectious drug-resistant TB and drug-susceptible TB case, and this may have led to misclassification of presumed drug-susceptible TB in some patients who should have been classified as presumed drug-resistant TB. The low proportion of patients who died and were LTFU in our cohorts could also limit the statistical power of the study. Although the definition of mortality used in this study has followed the current WHO guidelines as all-cause mortality before starting or during the course of treatment [18], the differentiation of death due to TB from other causes along with *post mortem* evidence could provide a more accurate characterisation of TB-related mortality. In addition, given the details on liver function tests and clinical features of DILI are not registered in the Netherlands Tuberculosis Register, further classification of symptomatic *versus* asymptomatic DILI cannot be presented.

In conclusion, this study demonstrates a high rate of successful treatment outcome in children and adolescents treated for TB in the Netherlands from 1993 to 2018. Specific risk groups for mortality, LTFU and unfavourable outcome have been identified for further development of early interventions to support these patients once diagnosed with TB.

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